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Synthesis of a New Enantiomerically Pure Constrained Homoserine.

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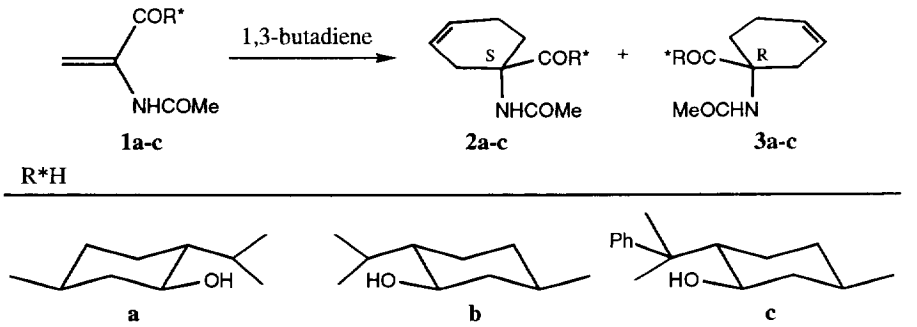
Abstract: The use of the Diels-Alder reaction between 1,3-butadiene and chiral 2-acetamidoacrylates as the key step followed by stereocontrolled transformations allows the synthesis of *(1S, 3R)*-1-amino-3-hydroxycyclohexanecarboxylic acid, a new type of constrained homoserine, with an excellent overall yield. Copyright © 1996 Elsevier Science Ltd

Whereas the asymmetric synthesis of α-amino acids has been a matter of longstanding interest[1], the asymmetric synthesis of conformationally constrained α-amino acids has only attracted significant attention over the last few years when it was recognised that their incorporation into peptides is a powerful approach to generating structurally defined peptides as conformational probes and bioactive agents[2]. In this context and as a part of our research project on the asymmetric synthesis of new, non-proteinogenic and unusual, conformationally restricted α-amino acids, we have developed a method involving the use of chiral 2-acetamidoacrylates as dienophiles as a good procedure for the synthesis of 2-aminonorbornane-2-carboxylic acids when they were reacted with cyclopentadiene allowing the synthesis of cycloaliphatic amino acids with very good yields and selectivities[3].

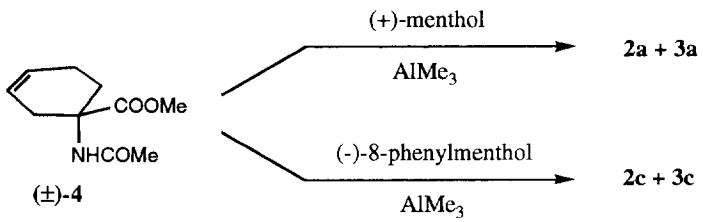
Very recently we have extended the method by using the methyl 2-acetamidoacrylate as a dienophile with 1,3-butadiene such that it is possible to obtain the corresponding cycloadducts with good yields and that the amido group can be used to effect direct hydroxylation through the iodo-oxazine intermediate to obtain a new type of constrained homoserine in a racemic form[4]. Therefore, due to the varied biological activities displayed by hydroxylated amino acids, in particular γ-hydroxy-α-amino acids, which can be found in a number of natural products[5], we would like to report now the extension of this methodology to the asymmetric synthesis of this new constrained homoserine.

The chiral dienophiles **1a-c** were obtained, according to a previously reported procedure[6], by the reaction of methyl 2-acetamidoacrylate with (+)-menthol, (-)-menthol and (-)-8-phenylmenthol in the presence of trimethylaluminium and, later, were reacted with 1,3-butadiene under a variety of conditions (Scheme 1).



Scheme 1

In order to find an appropriate method for analyzing the results of the Diels-Alder reactions, the cycloadducts **2a** + **3a** and **2c** + **3c** were prepared by an alternative synthetic route, by the transesterification of the racemic methyl 1-acetamido-3-cyclohexene-1-carboxylate **4** with the corresponding chiral auxiliary, following the same procedure described for the synthesis of the dienophiles. Cycloadduct **4** was obtained in good yield from the Diels-Alder reaction between methyl 2-acetamidoacrylate and an excess of 1,3-butadiene in methylene chloride at room temperature, using titanium tetrachloride as a catalyst[4] (Scheme 2). In this way, the results of the Diels-Alder reactions of 1,3-butadiene with chiral dienophiles were determined by ^{1}H-NMR (**1a**, **1b** and **1c**) and HPLC (**1c**).



Scheme 2

As the absolute configurations of the Diels-Alder cycloadducts are unknown, the crude product of the most selective cycloaddition between dienophile **1c** and 1,3-butadiene was purified by column chromatography and recrystallised to give the pure diastereoisomer **2c**, whose absolute configuration was established by X-ray analysis[7] (Figure 1).

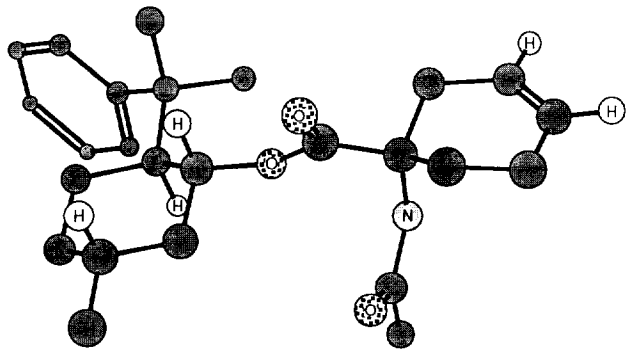


Figure 1

The results obtained in the Diels-Alder reactions are given in Table 1 and show the dependence of the

reaction rate on the nature of the Lewis acid used. In the absence of a catalyst or when the catalyst was $AlCl_2Et$ no reaction occurred. The best conversions were achieved when $TiCl_4$ was used as a catalyst (entries 1, 7, 13, 15) in a ratio $TiCl_4$/dienophile = 1.0. An increase in the selectivity when working at lower temperatures was not observed. Furthermore, under these conditions the cycloaddition rate was very low.

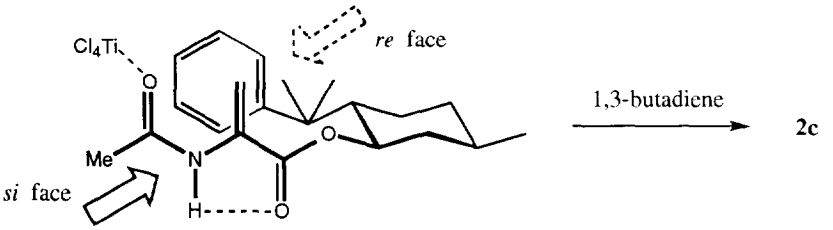
Table 1. Results Obtained from the Diels-Alder Cycloadditions between Dienophiles **1a-c** and 1,3-butadiene.

Entry	Dienophile[a]	Lewis Acid (eq)	T(°C)	t(d)	convn(%)[b]	**2a/3a**[c]	**2b/3b**[c]	**2c/3c**[c]
1	**1a**	$TiCl_4$(1.0)	0	9	73	30:70		
2	**1a**	$TiCl_4$(1.0)	-25	10	45	28:72		
3	**1a**	$TiCl_4$(1.5)	-25	10	51	26:74		
4	**1a**	$TiCl_4$(2.0)	-25	7	53	31:69		
5	**1a**	$TiCl_4$(0.5)	-25	10	-	-		
6	**1a**	$TiCl_4$(1.5)	0	6	68	30:70		
7	**1a**	$TiCl_4$(1.0)	25	4	82	29:71		
8	**1a**	$SnCl_4$(1.0)	0	10	8	-		
9	**1a**	$AlCl_2Et$(1.0)	25	10	-	-		
10	**1a**	$AlCl_3$(1.0)	25	10	-	-		
11	**1a**	-	25	10	-	-		
12	**1b**	$TiCl_4$(1.0)	0	9	71		71:29	
13	**1b**	$TiCl_4$(1.0)	25	5	80		70:30	
14	**1c**	$TiCl_4$(1.0)	0	9	28			99:1[d]
15	**1c**	$TiCl_4$(1.0)	25	6	91			99:1[d]

[a]All reactions were carried out in CH_2Cl_2 with a ratio diene/dienophile=12.0 and a dienophile concentration of 0.05 mmol/mL. [b]Determined by HPLC using a Hypersil® Silica column (5 µm, 4.6 mm i. d. x 250 mm) and monitored, at 200 nm, using a diode array detector. [c]See ref. 8. [d]Diastereofacial selectivity were confirmed by HPLC using a 40:60 hexane-^{t}butylmethyl ether mixture as the mobile phase and a flow rate of 2.0 mL/min. Retention times: **1c** = 2.52 min, **2c** = 6.89 min, **3c** = 7.87 min.

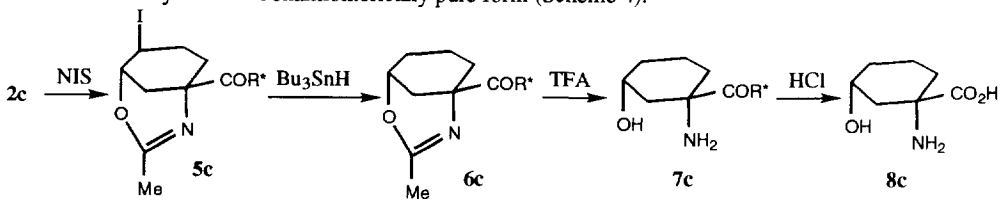
As expected, the diastereofacial selectivity depends on the nature of the chiral auxiliary. The best selectivity results were obtained when (-)-8-phenylmenthol was used, since only one diastereoisomer was observed by HPLC or ^{1}H-NMR but, it was necessary to work at room temperature to increase the reaction rate. The sense of face selectivity is the same as that observed for (-)-menthol and contrary to that for (+)-menthol.

These results and the stereochemical control agree with the model previously reported by us for the cycloaddition of (-)- and (+)-menthyl 2-acetamidoacrylates **1a,b** with cyclopentadiene[3]. This model is similar to that proposed by Oppolzer and Corey[9] for the Diels-Alder cycloaddition between chiral acrylates and several dienes. Thus, it is expected that the preferential coordination of the catalyst with the amido group[10] enforces the formation of the intramolecular hydrogen bond, favouring the antiplanar enoate conformation[11]. For this intermediate, as depicted in scheme 3, the acrylate moiety should ideally be positioned to maximise attractive interactions with the aromatic portion of the chiral auxiliary, shielding the *re* face of the double bond[12]. Indeed, the high diastereoselectivity observed can be explained by the preferential approach of the diene to the *si* face of the double bond.



Scheme 3

Starting from the major cycloadduct of the most selective Diels-Alder reaction **2c** (entry 15) and following a recently published[13] straightforward synthetic method, consisting of the directed hydroxylation of **2c** through a dihydro-1,3-oxazine intermediate, we have synthesised the homoserine analogue *(1S, 3R)* -1-amino-3-hydroxy-1-cyclohexanecarboxylic acid in enantiomerically pure form (Scheme 4).



Scheme 4

Cycloadduct **2c** was treated with N-iodosuccinimide to afford the (-)-8'-phenylmenthyl 3-methyl-*exo*-8-iodo-2-oxa-4-azabicyclo[3.3.1]non-3-ene-5-carboxylate **5c** in quantitative yield, allowing direct hydroxylation in a syn relationship to the amide group. The iodo-oxazine intermediate **5c**, purified by rmoving N-succinimide by extraction with a 10% aqueous NaOH solution, was easily deiodinated to compound **6c** using tributyltin hydride in methylene chloride at 40 °C. The reaction was quantitative but it was necessary to remove organotin compounds by silica gel column chromatography. Treatment of oxazine **6c** with trifluoroacetic acid in a solution of tetrahydrofuran-water at 80 °C for 8 h gave the corresponding (-)-8'-phenylmenthyl γ-hydroxy-α-aminocyclohexane-α-carboxylate **7c**, which was subsequently hydrolysed by the action of a 6N aqueous HCl solution under reflux, allowing the obtention of the desired chiral γ-hydroxy-α-amino acid as the hydrochloride salt. Further addition of propylene oxide in ethanol yielded the optically active amino acid **8c**, in which amino and hydroxy groups are in a syn relationship.

In summary, we have studied the asymmetric Diels-Alder cycloadditions of chiral 2-acetamidoacrylates with 1,3-butadiene demonstrating the different behaviour of these dienophiles with a diene less reactive than cyclopentadiene or 2,3-dimethyl-1,3-butadiene. We have obtained excellent diastereoselectivities by using (-)-8-phenylmenthol as a chiral auxiliary, when the reaction was catalysed by $TiCl_4$. These results could be exploited to synthesise a conformationally restricted, homoserine analogue, γ-hydroxy-α-amino acid in enantiomerically pure form.

Further work is in progress in order to obtain new families of optically active amino acids starting from the asymmetric Diels-Alder cycloadditions of this kind of dienophile.

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EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed by using Silica gel 60 (230-400 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Bruker ARX-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard and deuterated water or methanol with tetramethylsilane as the external standard using a

coaxial microtube (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi 530 and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values. Optical rotations were measured in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively.

Asymmetric Diels-Alder Cycloadditions. General Procedure.

The catalyst was added, under an inert atmosphere, to a solution of chiral dienophile **1a-c** (1.0 mmol) in CH_2Cl_2 (20 mL). After being stirred for 1 h at room temperature, the solution was cooled to the reaction temperature (Table 1) and a solution of 1,3-butadiene (648 mg, 12.0 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred for the time reported in Table 1 and then quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$. The mixture was filtered and the filtrate analyzed by HPLC or ^{1}H-NMR following removal of the solvent.

Alternative Synthesis of Chiral Cycloadducts. General Procedure.

Chiral alcohol (**1a,c**, 1 mmol) was dissolved in toluene (5 mL) in a dried, argon-filled two-neck round-bottom flask fitted with a stirrer, reflux condenser and septum joint. A 2.0 M solution of trimethylaluminium in hexane (0.55 mL, 1.1 mmol) was added through the septum at a moderate rate. The solution was stirred at 0 °C for 30 min. A solution of (±)-methyl 1-acetamido-3-cyclohexene-1-carboxylate **4** (291 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was then added through the septum at a moderate rate and the solution was stirred at 80 °C for 96 h. In the case of **1c** a further addition of methyl ester **4** (291 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was made and the solution was then stirred at 80 °C for 48 h. The reaction was quenched by addition of solid $Na_2CO_3 \cdot 10H_2O$ and filtered. The solvent was evaporated and the crude products were chromatographed on a silica gel column.

***(1'S,2'R,5'S)*-Menthyl *(1S)* and *(1R)*-1-Acetamido-3-cyclohexene-1-carboxylate. (2a+3a).**

Purified by silica gel column chromatography (hexane/EtOAc, 3:7). Isolated yield 101 mg (52%) as an oil.

^{1}H-NMR($CDCl_3$): δ: 0.70-2.32(m, 38H); 0.75(d, 3H, *J*=6.0); 0.77(d, 3H, *J*=6.0); 0.88(d, 6H, *J*=6.5); 0.90(d, 6H, *J*=6.5); 1.98(s, 3H); 1.99(s, 3H); 2.32-2.43(m, 2H); 2.52-2.63(m, 2H); 4.64-4.74(m, 2H); 4.56-5.79(m, 6H).

^{13}C-NMR($CDCl_3$): δ: 15.9, 20.8, 21.8, 21.9, 22.0, 23.1, 25.9, 26.6, 26.8, 31.3, 33.9, 34.2, 40.3, 57.1, 75.0, 75.1, 122.3, 122.5, 127.3, 127.4, 169.7, 169.8, 172.9, 173.0.

***(1'R,2'S,5'R)*-8'-Phenylmenthyl *(1S)* and *(1R)*-1-Acetamido-3-cyclohexene-1-carboxylate. (2c+3c).**

Purified by silica gel column chromatography (hexane/EtOAc, 1:1). Isolated yield 41 mg (10%) as an oil.

^{1}H-NMR($CDCl_3$): δ: 0.75-2.43(m, 28H); 0.86(d, 3H, *J*=6.0); 0.87(d, 3H, *J*=6.0); 1.19-1.39(brs, 12H); 1.93(s, 3H); 1.94(s, 3H); 4.78-4.89(m, 2H); 5.27(brs, 1H); 5.39(brs, 1H); 5.47-5.78(m, 4H); 7.11-7.39(m, 10H).

^{13}C-NMR($CDCl_3$): δ: 21.6, 21.7, 23.2, 25.7, 27.1, 27.9, 29.7, 31.3, 32.7, 33.8, 34.6, 39.8, 40.0, 40.9, 41.9, 49.8, 49.9, 57.0, 76.4, 76.5, 121.8, 122.6, 124.9, 125.0, 125.5, 125.7, 126.8, 127.7, 127.9, 128.0, 151.6, 169.6, 172.9, 173.0.

(+)-*(1'R,2'S,5'R)*-8'-Phenylmenthyl *(1S)*-1-Acetamido-3-cyclohexene-1-carboxylate. 2c.

This compound was obtained from (-)-8-phenylmenthyl 2-acetamidoacrylate **1c** (686 mg, 2.0 mmol) following the general procedure described above for the asymmetric Diels-Alder reaction (1 eq. $TiCl_4$, r.t., 6 days). The

reaction mixture was treated with $Na_2CO_3 \cdot 10H_2O$, filtered and the solvent removed. The major cycloadduct **2c** was purified by silica gel column chromatography, eluting with hexane-EtOAc (1:1). Compound **2c** was obtained as a white solid in 80% yield. Mp: 165-8 °C. $[\alpha]^{25}_D$(c = 17.5, $CHCl_3$) = +43.6.

Found C: 75.47, H: 3.64, N: 8.79

Anal. Calc. for $C_{25}H_{35}NO_3$ C: 75.53, H: 3.52, N: 8.87

^{1}H-NMR ($CDCl_3$) δ: 0.78-2.15(m, 12H); 0.85(d, 3H, *J*=6.6); 1.23(s, 3H); 1.38(s, 3H); 1.93(s, 3H); 2.20-2.31(m, 1H); 2.36-2.45(m, 1H); 4.83('t'd, 1H, *J*=10.5, *J*=4.2); 5.32(brs, 1H); 5.47-5.55(m, 1H); 5.68-5.77(m, 1H); 7.11-7.35(m, 5H).

^{13}C-NMR ($CDCl_3$) δ: 21.7, 21.8, 23.2, 25.7, 27.1, 27.9, 29.7, 31.3, 33.8, 34.6, 40.0, 41.0, 49.4, 57.0, 76.4, 121.8, 125.0, 125.7, 127.7, 127.9, 151.6, 169.6, 173.0.

(+)-*(1'R,2'S,5'R)*-8'-Phenylmenthyl *(1S,5S,8S)*-3-Methyl-*exo*-8-iodo-2-oxa-4-azabicyclo [3.3.1]non-3-ene-5-carboxylate. 5c.

Cycloadduct **2c** (650 mg, 1.63 mmol) was dissolved in CH_2Cl_2 (33 mL) and then N-iodosuccinimide (368 mg, 1.63 mmol) was added. After stirring for 14 h, at room temperature, the mixture was treated with a 10% aqueous NaOH solution (3 x 20 mL), dried and the solvent evaporated to give quantitatively iodo-oxazine **5c** as an oil. $[\alpha]^{25}_D$(c = 30.0, $CHCl_3$) = +30.2.

Found C: 57.43, H: 6.61, N: 2.54, I: 24.33

Anal. Calc. for $C_{25}H_{34}NO_3I$ C: 57.36, H: 6.54, N: 2.67, I: 24.26

^{1}H-NMR($CDCl_3$): δ: 0.84(d, 3H, *J*=6.6); 0.92-1.10(m, 2H); 1.30(s, 3H); 1.41(s, 3H); 1.42-1.52(m, 3H); 1.67-1.77(m, 2H); 1.78-2.09(brs, 9H); 2.69(dd, 1H, *J*=13.8, *J*=1.3); 4.48-4.53(m, 2H); 4.86-4.97(m, 1H); 7.12-7.18(m, 1H); 7.25-7.32(m, 4H).

^{13}C-NMR($CDCl_3$): δ: 21.0, 21.7, 24.9, 25.8, 27.1, 27.7, 28.3, 28.8, 29.3, 31.2, 34.4, 40.2, 41.4, 49.9, 57.2, 74.2, 75.9, 125.3, 125.6, 128.0, 150.8, 158.1, 172.2.

(+)-*(1'R,2'S,5'R)*-8'-Phenylmenthyl *(1R,5S)*-3-Methyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-5-carboxylate. 6c.

Tributyltin hydride (0.79 mL, 2.96 mmol) was added to a solution of iodo-oxazine **5c** (778 mg, 1.48 mmol) in dry CH_2Cl_2 (65 mL) kept under inert atmosphere. After stirring for 6 h, at 40 °C, the solvent was evaporated and the residue was chromatographed on silica gel (hexane/EtOAc, 6:4) to afford 550 mg of dihydro-1,3-oxazine **6c** as an oil (92%). $[\alpha]^{25}_D$(c = 16.5, $CHCl_3$) = +10.0.

Found C: 75.45, H: 8.99, N: 3.61

Anal. Calc. for $C_{25}H_{35}NO_3$ C: 75.51, H: 8.87, N: 3.52

^{1}H-NMR($CDCl_3$): δ: 0.83(d, 3H, *J*=6.3); 0.97-1.10(m, 2H); 1.23(s, 3H); 1.34(s, 3H); 1.35-2.10(m, 17H); 4.41-4.47(m, 1H); 4.82-4.92(m, 1H); 7.11-7.18(m, 1H); 7.24-7.34(m, 4H).

^{13}C-NMR($CDCl_3$): δ: 21.5, 21.7, 25.9, 26.8, 27.0, 28.2, 29.9, 31.2, 31.5, 33.2, 34.5, 40.1, 41.4, 49.6, 57.2, 70.7, 75.6, 125.1, 125.6, 128.0, 151.1, 159.6, 173.7.

(+)-*(1'R,2'S,5'R)*-8'-Phenylmenthyl *(1S,3R)*-1-Amino-3-hydroxy-1-cyclohexanecarboxylate. 7c.

Compound **6c** (550 mg, 1.38 mmol) was dissolved in 3:1 tetrahydrofuran-water (60 mL) and trifluoroacetic acid (3.03 g, 26.6 mmol) was added. The reaction was then heated at 80 °C for 36 h to give the corresponding γ-

hydroxy-α-amino ester **7c** in 95% yield. In order to remove most of the trifluoroacetic acid, the solvent was eliminated under reduced pressure, the oily residue was then dissolved in diethyl ether and the solvent and the residual trifluoroacetic acid distilled off *in vacuo*. This operation was repeated to ensure complete removal of the trifluoroacetic acid. Mp: 168-9 °C. $[\alpha]^{25}_D$(c = 22.0, $CHCl_3$) = +11.7.

Found C: 74.06, H: 9.53, N: 3.84

Anal. Calc. for $C_{23}H_{35}NO_3$ C: 73.94, H: 9.45, N: 3.75

^{1}H-NMR(CD_3OD): δ: 1.61-1.69(m, 3H); 1.71-2.70(m, 15H); 1.90(s, 3H); 2.02(s, 3H); 3.04-3.13(m, 1H); 4.78-4.83(m, 1H); 5.58-5.70(m, 4H); 7.84-7.89(m, 1H); 7.99-8.11(m, 4H).

^{13}C-NMR(CD_3OD): δ: 13.3, 14.8, 21.3, 24.3, 27.0, 29.2, 30.0, 30.1, 30.8, 31.9, 34.7, 39.8, 41.6, 60.1, 64.8, 78.5, 125.4, 125.8, 128.7, 152.3, 171.3.

(+)-*(1S,3R)*-1-Amino-3-hydroxy-1-cyclohexanecarboxylic Acid. 8c.

The trifluoroacetate derivative of compound **7c** (260 mg, 0.54 mmol) was dissolved in 6 N HCl (20 mL) and refluxed for 24 h. The solvent was evaporated, the aminoacid hydrochloride residue was dissolved in EtOH (15 mL) and propylene oxide (5 mL) was added. The mixture was refluxed for 2 h and partially precipitated. After removal of EtOH, the residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge which, after removal of water, gave α-amino acid **8c** in 75% yield as a white solid. $[\alpha]^{25}_D$(c = 7.7, 10% HCl in H_2O) = +5.4.

Found C: 52.92, H: 8.30, N: 8.92

Anal. Calc. for $C_7H_{13}NO_3$ C: 52.80, H: 8.23, N: 8.80

^{1}H-NMR(D_2O-TFA): δ: 1.69-2.00(m, 6H); 2.1-2.22(m, 1H); 2.31(dd,1H, *J*=14.2, *J*=2.5); 4.25-4.32(m, 1H).

^{13}C-NMR(D_2O-TFA): δ: 15.7, 30.5, 31.0, 36.0, 59.6, 65.2, 173.6.

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